AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph beginning on page 10, line 10, with the following:

The compositions provided herein can further comprise a therapeutic agent (e.g., a cytokine, an anti-cancer agent, an adjuvant, etc.). In some embodiments the adjuvant is alum, monophosphoryl lipid A, a saponin, an immunostimulatory oligonucleotide, incomplete Freund's adjuvant, complete Freund's adjuvant, ~~montanide~~ MONTANIDE™, vitamin E, a water-in-oil emulsion[[s]] prepared from a biodegradable oil, Quil A, a MPL™ and mycobacterial cell wall skeleton combination, ENHANZYN™, CRL-1005, L-121, alpha-galactosylceramide or a combination thereof.

Please replace the paragraph beginning on page 27, line 32, with the following:

Figure 13 depicts the cloning protocol for IgG1 antibody cloning into pcDNA (SEQ ID NOs: 34-37).

Please replace the paragraph beginning on page 29, line 22, with the following:

FIG. 35 shows the results of the comparison of the fully human anti-PSMA antibodies 4.40.1, 4.49.1, 051 and 006 and the murine anti-PSMA antibody 3.9 performed using ~~Biacore~~BIACORE™ analysis.

Please replace the paragraph beginning on page 37, line 7, with the following:

In some cases where a high salt concentration is used to promote or preserve PSMA dimerization, the salt concentration can be diluted to within a physiologically acceptable range suitable for parenteral use prior to administration. As an example, the salt concentration can be diluted with an adjuvant or a diluent. Diluents and adjuvants are both well known in the art. An adjuvant is a substance which potentiates the immune response. Specific examples of adjuvants include monophosphoryl lipid A (MPL™, SmithKline Beecham); saponins including QS21 (SmithKline Beecham); immunostimulatory oligonucleotides (e.g., CpG oligonucleotides described by Kreig et al., Nature 374:546-9, 1995); incomplete Freund's adjuvant; complete Freund's adjuvant; montanide; vitamin E and various water-in-oil emulsions prepared from biodegradable oils such as squalene and/or tocopherol, Quil A, MPL™ and cell wall skeleton from mycobacterium combinations such as

ENHANZYN™ (Corixa Corporation, Hamilton, MT), CRL-1005, L-121, alpha-galactosylceramide (Fujii et al., J. Exp. Med., 2003, Jul. 21; 198(2): 267-79) and combinations thereof. A preferred adjuvant is alum. Other diluents include water suitable for injection, saline, PBS, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan and mixtures thereof.

Please replace the paragraph beginning on page 38, line 30, with the following:

The effect of free amino acids on the dimeric state of rsPSMA (2 mg/ml in PBS+) dialyzed into 20mM sodium acetate and 150mM NaCl at a pH of about 6 was also tested. In general it was found that free amino acids did not have a strong negative effect on dimer association of PSMA and/or column recovery, with the exception of histidine, glutamic acid and aspartic acid used individually at the specific experimental conditions. Therefore, the formulations provided herein can also include a free amino acid or combination of free amino acids, provided that the free amino acid does not have a negative effect that outweighs the dimeric association promoting or preserving nature of the specific formulation. Such free amino acids can be naturally occurring, modified or non-naturally occurring free amino acids (i.e., compounds that do not occur in nature but that can be incorporated into a polypeptide chain; see, for example, [[http://www.]]cco.caltech.edu/~dadgrp/Unnatstruct.gif, which displays structures of non-natural amino acids that have been successfully incorporated into functional ion channels). Modified or non-naturally occurring free amino acids also include but are not limited to 2-aminoadipic acid; 3-aminoadipic acid; beta-alanine, beta-aminopropionic acid; 2-aminobutyric acid; 4-aminobutyric acid, piperidinic acid; 6-aminocaproic acid; 2-aminoheptanoic acid; 2-aminoisobutyric acid; 3-aminoisobutyric acid; 2-aminopimelic acid; 2, 4-diaminobutyric acid; desmosine; 2,2'-diaminopimelic acid; 2,3-diaminopropionic acid; N-ethylglycine; N-ethylasparagine; hydroxylysine; allo-hydroxylysine; 3-hydroxyproline; 4-hydroxyproline; isodesmosine; allo-isoleucine; N-methylglycine, sarcosine; N-methylisoleucine; 6-N-methyllysine; N-methylvaline; norvaline; norleucine and ornithine. In particular, free amino acids that do not have a negative effect on dimeric association of

PSMA and/or column recovery include those that are non-acidic. Examples of these non-acidic free amino acids include glycine, proline, isoleucine, leucine, alanine and arginine.

Please replace the paragraph beginning on page 47, line 28, with the following:

The term "high stringency conditions" as used herein refers to parameters with which the art is familiar. Nucleic acid hybridization parameters may be found in references that compile such methods, e.g. *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989, or *Current Protocols in Molecular Biology*, F. M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. One example of high-stringency conditions is hybridization at 65°C in hybridization buffer (3.5X SSC, 0.02% ~~Ficoll~~ FICOLL™, 0.02% polyvinyl pyrrolidone, 0.02% Bovine Serum Albumin, 2.5 mM NaH_2PO_4(pH7), 0.5% SDS, 2 mM EDTA). SSC is 0.15M sodium chloride/0.015M sodium citrate, pH7; SDS is sodium dodecyl sulphate; and EDTA is ethylenediaminetetracetic acid. After hybridization, a membrane upon which the nucleic acid is transferred is washed, for example, in 2X SSC at room temperature and then at 0.1-0.5X SSC/0.1X SDS at temperatures up to 68°C.

Please replace the paragraph beginning on page 50, line 22, with the following:

Mammalian lymphocytes typically are immunized by in vivo immunization of the animal (e.g., a mouse) with the desired protein or polypeptide, e.g., with PSMA in the present invention. Such immunizations are repeated as necessary at intervals of up to several weeks to obtain a sufficient titer of antibodies. Once immunized, animals can be used as a source of antibody-producing lymphocytes. Following the last antigen boost, the animals are sacrificed and spleen cells removed. Mouse lymphocytes give a higher percentage of stable fusions with the mouse myeloma lines described herein. Of these, the BALB/c mouse is preferred. However, other mouse strains, rabbit, hamster, sheep and frog may also be used as hosts for preparing antibody-producing cells. See; Goding (in Monoclonal Antibodies: Principles and Practice, 2d ed., pp. 60-61, Orlando, Fla., Academic Press, 1986). In particular, mouse strains that have human immunoglobulin genes inserted in the genome (and which cannot produce mouse immunoglobulins) are preferred. Examples include the ~~HuMAb~~ HUMAB™ mouse strains produced by Medarex/GenPharm International, and the ~~XenoMouse~~ XENOMOUSE™ strains produced by Abgenix. Such mice produce fully human

immunoglobulin molecules in response to immunization.

Please replace the paragraph beginning on page 54, line 1, with the following:

Fully human monoclonal antibodies also can be prepared by immunizing mice transgenic for large portions of human immunoglobulin heavy and light chain loci. See, e.g., U.S. Pat. Nos. 5,591,669, 5,598,369, 5,545,806, 5,545,807, 6,150,584, and references cited therein, the contents of which are incorporated herein by reference. These animals have been genetically modified such that there is a functional deletion in the production of endogenous (e.g., murine) antibodies. The animals are further modified to contain all or a portion of the human germ-line immunoglobulin gene locus such that immunization of these animals results in the production of fully human antibodies to the antigen of interest. Following immunization of these mice (e.g., ~~XenoMouse~~ XENOMOUSE™ (Abgenix), ~~HuMAb~~ HUMAB™ mice (Medarex/GenPharm)), monoclonal antibodies are prepared according to standard hybridoma technology. These monoclonal antibodies have human immunoglobulin amino acid sequences and therefore will not provoke human anti-mouse antibody (HAMA) responses when administered to humans.

Please replace the paragraph beginning on page 56, line 18, with the following:

The testing of antibody cytolytic activity *in vitro* by chromium release assay can provide an initial screening prior to testing *in vivo* models. This testing can be carried out using standard chromium release assays. Briefly, polymorphonuclear cells (PMN), or other effector cells, from healthy donors can be purified by ~~Ficoll~~FICOLL™ Hypaque density centrifugation, followed by lysis of contaminating erythrocytes. Washed PMNs can be suspended in RPMI supplemented with 10% heat-inactivated fetal calf serum and mixed with ^{51}Cr labeled cells expressing PSMA, at various ratios of effector cells to tumor cells (effector cells:tumor cells). Purified anti-PSMA IgGs can then be added at various concentrations. Irrelevant IgG can be used as negative control. Assays can be carried out for 0-120 minutes at 37°C. Samples can be assayed for cytolysis by measuring ^{51}Cr release into the culture supernatant. Anti-PSMA monoclonal antibodies can also be tested in combinations with each other to determine whether cytolysis is enhanced with multiple monoclonal antibodies.

Please replace the paragraph beginning on page 59, line 1, with the following:

Other preferred antibodies include antibodies that specifically (i.e., selectively) bind to an epitope on PSMA defined by a second antibody. To determine the epitope, one can use standard epitope mapping methods known in the art. For example, fragments (peptides) of PSMA antigen (preferably synthetic peptides) that bind the second antibody can be used to determine whether a candidate antibody binds the same epitope. For linear epitopes, overlapping peptides of a defined length (e.g., 8 or more amino acids) are synthesized. The peptides preferably are offset by 1 amino acid, such that a series of peptides covering every 8 amino acid fragment of the PSMA protein sequence are prepared. Fewer peptides can be prepared by using larger offsets, e.g., 2 or 3 amino acids. In addition, longer peptides (e.g., 9-, 10- or 11-mers) can be synthesized. Binding of peptides to antibodies can be determined using standard methodologies including surface plasmon resonance (~~BIACORE~~ BIACORE™; see Example 22) and ELISA assays. For examination of conformational epitopes, larger PSMA fragments can be used. Other methods that use mass spectrometry to define conformational epitopes have been described and can be used (see, e.g., Baerga-Ortiz et al., *Protein Science* 11: 1300-1308, 2002 and references cited therein). Still other methods for epitope determination are provided in standard laboratory reference works, such as Unit 6.8 ("Phage Display Selection and Analysis of B-cell Epitopes") and Unit 9.8 ("Identification of Antigenic Determinants Using Synthetic Peptide Combinatorial Libraries") of *Current Protocols in Immunology*, Coligan et al., eds., John Wiley & Sons. Epitopes can be confirmed by introducing point mutations or deletions into a known epitope, and then testing binding with one or more antibodies to determine which mutations reduce binding of the antibodies.

Please replace the paragraph beginning on page 61, line 7, with the following:

Agents that act on the tumor vasculature can include tubulin-binding agents such as combrestatin A4 (Griggs et al., *Lancet Oncol.* 2:82, 2001), angiostatin and endostatin (reviewed in Rosen, *Oncologist* 5:20, 2000, incorporated by reference herein) and interferon inducible protein 10 (U.S. Pat. No. 5,994,292). A number of antiangiogenic agents currently in clinical trials are also contemplated. Agents currently in clinical trials include: 2ME2, Angiostatin, ~~Angiozyme~~ ANGIOZYME™, Anti-VEGF RhuMAb, Apra (CT-2584), ~~Avicine~~ AVICINE™, Benefin, BMS275291, Carboxyamidotriazole, CC4047, CC5013, CC7085, CDC801, CGP-41251 (PKC 412),

CM101, Combretastatin A-4 Prodrug, EMD 121974, Endostatin, Flavopiridol, Genistein (GCP), Green Tea Extract, IM-862, ImmTher, Interferon alpha, Interleukin-12, ~~Iressa~~ IRESSA™ (ZD1839), Marimastat, ~~Metastat~~ METASTAT™ (Col-3), ~~Neovastat~~ NEOVASTAT™, Octreotide, Paclitaxel, Penicillamine, ~~Photofrin~~ PHOTOFRIN™, ~~Photopoint~~ PHOTOPOINT™, PI-88, Prinomastat (AG-3340), PTK787 (ZK22584), RO317453, Solimastat, Squalamine, SU 101, SU 5416, SU-6668, Suradista (FCE 26644), Suramin (Metaret), Tetrathiomolybdate, Thalidomide, TNP-470 and ~~Vitaxin~~ VITAXIN™. [[a]] Additional antiangiogenic agents are described by Kerbel, J. Clin. Oncol. 19(18s):45s-51s, 2001, which is incorporated by reference herein. Immunomodulators suitable for conjugation to anti-PSMA antibodies include α-interferon, γ-interferon, and tumor necrosis factor alpha (TNFα).

Please replace the paragraph beginning on page 73, line 8, with the following:

Antigens, such as the PSMA dimers described herein, can be administered with one or more adjuvants to induce or enhance an immune response. An adjuvant is a substance which potentiates the immune response. Adjuvants of many kinds are well known in the art. Specific examples of adjuvants include monophosphoryl lipid A (MPL™, SmithKline Beecham); saponins including QS21 (SmithKline Beecham); immunostimulatory oligonucleotides (e.g., CpG oligonucleotides described by Kreig et al., *Nature* 374:546-9, 1995); incomplete Freund's adjuvant; complete Freund's adjuvant; ~~montanide~~ MONTANIDE™; vitamin E and various water-in-oil emulsions prepared from biodegradable oils such as squalene and/or tocopherol, Quil A, Ribi Detox, CRL-1005, L-121, and combinations thereof.

Please replace the paragraph beginning on page 86, line 6, with the following:

Mice having the ability to produce human antibodies (~~XenoMouse~~ XENOMOUSE™, Abgenix; Mendez et al., *Nature Genetics* 15:146, 1997) were immunized subcutaneously once or twice weekly with 5 X 10^6 LNCaP cells adjuvanted with alum or Titermax Gold (Sigma Chemical Co., St. Louis, Mo.). Animals were boosted twice with 10 μg of recombinant PSMA protein immunoaffinity captured onto protein G magnetic microbeads (Miltenyi Biotec, Auburn, CA). PSMA mAb 3.11 was used for capture. Splenocytes were fused with NSO myeloma cells and the hybridomas that resulted were screened as above by flow cytometry to detect clones producing antibodies reactive

with the extracellular portion of PSMA. One clone, 10.3 (PTA-3347), produced such antibodies.

Please replace the paragraph beginning on page 110, line 8, with the following:

Example 22: Binding Affinity Using ~~Biacore 3000~~ BIACORE™ 3000

Please replace the paragraph beginning on page 110, line 9, with the following:

To determine the kinetics and affinity of the antibodies, the antibodies in crude supernatants, in purified form and in bifunctional chelate modified forms were analyzed using a ~~Biacore 3000~~ BIACORE™ 3000 instrument (Biacore Inc., Piscataway, N.J.). ~~Biacore 3000~~ BIACORE™ 3000 is a fully automated surface plasmon resonance (SPR)-based biosensor system that is designed to provide real-time kinetic data from assay formats that require no tags or labeling of compounds for biomolecular interactions. It is ideal for screening crude supernatants.

Please replace the paragraph beginning on page 110, line 15, with the following:

The streptavidin-coated sensor chips (SA chips, Biacore) were used to capture biotinylated anti-human IgG antibody (Sigma, St. Louis, MO). The entire sensor chip surface was conditioned with five injections of conditioning solution (1 M NaCl, 50 mM NaOH) and equilibrated with PBS buffer containing 0.005% polysorbate 20. Two to three thousand resonance units (RU) of biotinylated anti-human IgG antibody (Sigma) were immobilized onto the SA chip followed by an injection of regeneration buffer (glycine-HCl, pH 2.2). Antibodies in supernatants were diluted to 2 μg/mL in PBS buffer and captured onto one anti-human IgG flow cell, while isotype-matched control human antibody (Sigma) was similarly captured on a second flow cell. rsPSMA at different concentrations in PBS buffer was flowed over the cells at 30 μL/min for 3 min in an "association phase" followed by a "dissociation phase" for 10 min. SPR was monitored and displayed as a function of time. For each antibody at one concentration, the chip was regenerated and equilibrated. Examples of the analysis of antibody PRGX1-XG-006 in association phase and dissociation phase at different concentrations of rsPSMA from 100 nM to 6.25 nM are shown in Fig. 34. Thermodynamic and kinetic rate constants of binding were calculated using the ~~Biacore~~ BIACORE™ Evaluation software. For example, the affinity of XG-006 antibodies in a supernatant to rsPSMA was determined to be $4.92X10^{-10}$ M with a K_a of $1.3X10^5$ $M^{-1}s^{-1}$ and a K_d of $6.4X10^{-5}$ s^{-1}. Selective data for several

human PSMA antibodies in crude supernatant, purified form, and modified with bifunctional chelate is listed in Table 5 for comparison.

Please replace the paragraph beginning on page 111, line 12, with the following:

A comparison of the fully human antibodies 4.40.1, 4.49.1, 051 and 006 and the murine antibody 3.9 was performed by ~~Biacore~~BIACORE™]. For each antibody for comparison, response was normalized to 100 RU. The graph of time vs. response difference for these antibodies is given in Fig. 35. The binding affinities for these antibodies were determined to be 6.1, 6.7, 5.8, 4.8 and 13.7X10^{-10}M, respectively.

Please delete table 6, beginning on page 112, line 11, and replace with the following:

	Ab Conc (µg/mL)		Binding to 3T3-PSMA (FACS)					~~Biacore~~BIACORE™ studies		
Supernatant	PGNX	Lysate EIA	PGNX FACS	AVG Max binding	AVG EC50	C4.2 FACS	Anti-PSMA Western	KD, M-1 (x 10^{-10})	Ka, M-1s-1 (x 10^{6})	Kd, s-1 (x 10-5)
PRGX1-XG1-026	4.7	ND[1]	ND	148	2.4	ND	Conf.[2]	2.0	1.5	2.9
4.4.1	4.7	0.08	7	8	ND	5.2	Conf.	4.2	2.3	9.7
PRGX1-XG1-006	1.8	0.39	114	183	3.4	9.5	Conf.	4.8	1.3	6.4
PRGX1-XG1-051	3.5	0.48	83	202	2.0	9.9	Conf.	5.8	1.4	8.2
4.40.1	4.3	0.33	53	163	2.3	10.8	Conf.	6.1	2.1	12.5
4.49.1	2.6	0.36	362	162	0.9	16.2	Conf.	6.7	3.1	20.7
4.292.1	2.7	0.18	75	195	6.0	9.2	Conf.	6.8	1.2	8.5
4.304.1	4.1	0.39	92	184	9.1	8.4	Conf.	8.7	1.4	12.5
4.232.1	2.4	0.49	97	138	2.7	6.0	Linear[3]	9.4	1.5	13.8
4.153.1	5.9	0.29	279	182	5.3	14.8	Conf.	9.5	1.2	11.8
4.333.1	2.9	0.18	82	168	3.1	6.6	Conf.	11	0.7	8.5
PRGX1-XG1-077	3.9	0.45	392	227	6.0	12.4	Conf.	16	0.6	10.4
10.3	8.5	1.06	ND	ND	ND	ND	ND	19	1.9	36.4
pure 10.3		0.44	130	181	7.5	ND	Conf.	ND		
						4.7				
4.22.1	2.8	0.08	7	ND	ND	4.7	ND	*20*	*1.7*	*33*
4.248.1	3.5	0.37	7	ND	ND	4.1	Conf.	*27*	*1.0*	*28*
4.54.1	10	0.14	267	162	3.9	13.6	ND	30	1.9	56
4.7.1	5	0.23	156	141	1.6	10.2	Conf.	32	1.7	56
4.78.1	5.3	0.00	205	118	1.0	7.9	Conf.	*53*	*2.4*	*125*

4.48.1	4.9	0.06	14	ND	ND	7.7	ND	*62*	*0.9*	*59*
4.209.1	3.5	0.22	60	ND	ND	6.7	ND	*142*	*0.9*	*125*
4.177.1	1.1	0.15	**236**	**174**	**2.4**	**10.6**	ND	*155*	*0.6*	*93*
4.152.1	3.4	**0.38**	81	85	4.0	7.5	ND	*163*	*0.8*	*126*
4.28.1	4.2	0.04	**112**	155	4.2	**11.3**	ND	*167*	*1.2*	*192*
4.16.1	5.3	0.00	8	ND	ND	7.8	ND	*177*	*1.8*	*313*
4.360.1	1.5	0.02	**112**	130	**2.2**	7.9	ND	*197*	*1.0*	*201*
4.288.1	15.4	0.02	67	141	4.1	6.5	ND	*198*	*1.3*	*257*
4.219.2	0.5	**0.34**	69	ND	ND	5.9	ND	ND		
PRGX1-XG1-069	6.5	ND	ND	71	7.9	ND	ND	No Binding		
Murine 3.9								13.7	0.7	9.7
Control								6.34	2.24	14.2

[1] ND=not determined
[2] conf.=conformational epitope
[3] linear=linear epitope

Please replace the paragraph beginning on page 116, line 19, with the following:

A ~~Biacore 3000~~ BIACORE™ 3000 instrument was used to monitor, in real time, binding of rsPSMA dimer and monomer to anti-PSMA mAbs. Antibodies were immobilized at approximately 10,000 resonance units to CM5 sensor chips according to the manufacturer's instructions for amine coupling (Biacore, Inc., Piscataway, N.J.). A reference surface of isotype-matched antibody of irrelevant specificity was used as a background control. Binding experiments were performed at 25°C in PBS buffer with 0.005% [vol/vol] Surfactant P20. Purified rsPSMA dimer (50 nM) or monomer (100 nM) was passed over control and test flow cells at a flow rate of 5 μL/min. The sensor surface was regenerated with two pulses of 20 nM HCl.